

# Correction of Cavity-Induced Errors in Polarization Charges of Continuum Solvation Models

MAURIZIO COSSI,<sup>1</sup> BENEDETTA MENNUCCI,<sup>2</sup> JESUS PITARCH,<sup>3</sup>  
JACOPO TOMASI<sup>2</sup>

<sup>1</sup>*Dipartimento di Chimica, Università Federico II, Napoli, Italy*

<sup>2</sup>*Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, I-56100 Pisa, Italy*

<sup>3</sup>*Departamento de Química-Física, Universidad de Valencia, Valencia, Spain*

*Received 27 May 1997; accepted 2 January 1998*

**ABSTRACT:** We present a formal and numerical analysis of the errors related to the use of molecular cavities in the continuum description of solute–solvent electrostatic interactions. In this approximation the solvent response is fully described by an apparent charge distribution induced on the cavity surface. The latter is then discretized into a set of point charges that are generally affected by errors of different origin but all depending on the definition of the cavity boundaries, and the way its surface is partitioned. The numerical analysis is based on results obtained for a set of couples of neutral/anionic solutes obtained with various versions of PCM methods, exploiting different correction procedures, as well as with two recently developed continuum methods, complementing PCM. © 1998 John Wiley & Sons, Inc. *J Comput Chem* 19: 833–846, 1998

**Keywords:** continuum solvation models; *ab initio* calculations; solvation free energy; solute–solvent interactions; cavity errors

*Correspondence to:* J. Tomasi; e-mail: tomasi@dcc.unipi.it  
Contract/grant sponsor: Consiglio Nazionale delle Ricerche

## Introduction: Molecular Cavity in Solvation Models

**M**olecular systems dissolved in liquid phases are often described in terms of a “solute,” treated at an accurate level of description, and of a “solvent,” encircling the solute and treated at a lower level.

The effective QM Hamiltonian of this model must be provided with a solute–solvent interaction operator. Expressions are simpler when the solvent is described in terms of a continuous distribution, and the interaction operator is expressed in terms of response functions representing the effects of the perturbations, of various physical origins (electrostatic, repulsive, dispersive), induced on the medium by the solute.

To describe these interaction operators, one must define a *cavity*; that is, a portion of space in which the solvent density is set equal to zero and where the solute is accommodated. To reach a good description of solvent effects this cavity must be well modeled on the shape of the solute, as intuition suggests and calculations confirm. A possible strategy to get well-shaped cavities is to use interlocking spheres of appropriate radius centered on solute atoms or groups of atoms. This choice implies a marginal freedom in defining the details of this cavity, which will be exploited in the present study.

There are several ways of incorporating the solute–solvent interaction operator into the effective Hamiltonian. The large body of literature on this subject has been reviewed extensively in a study by Tomasi and Persico.<sup>1</sup> Here we shall only consider the approach based on the use of apparent charges on the cavity surface (ASC approach, according to the terminology of ref. 1), and, in particular to the realizations of this approach given in PCM (polarizable continuum model), a comprehensive procedure to study solvation effects we are currently developing.

In all ASC methods—particularly PCM—the apparent charge density on the cavity surface is described in terms of a finite set of point charges, each placed at the center of a small portion of the cavity, called *tessera*. The *tesserae* cover the whole cavity surface without overlaps or voids. Clearly this is just an approximation, giving rise to some errors, which will be referred to in the following as *discretization errors*.

The apparent point charges introduced here are addressed to describe the reaction field due to the solvent electrostatic response function. This is the most important term in studying solvation problems of chemical interests in polar solvents, even if there are other solute–solvent interactions that have always to be taken into account to reach the most correct description of solvent effects; indeed, in some specific cases, their role becomes quite important. In PCM all these terms are discretized; that is, calculated as sums over the surface *tesserae*. PCM is also the only ASC method that can introduce interaction terms of nonelectrostatic origin (dispersion and repulsion) into the effective Hamiltonian,<sup>1,2</sup> but in this study we completely neglect these contributions. We only remark that the discretization errors introduced for these terms are less severe than those for the electrostatic term; in fact, in the latter case, the main contribution to discretization errors is related to the intermediate step of self-polarization of the ASCs,<sup>3</sup> which, on the contrary, is absent in the former terms; this point will be better analyzed in the following.

Within the electrostatic approximation, the solvent response is determined by exploiting classical electrostatic formulas for a polarizable charge distribution,  $\rho_M$ , in the presence of a medium with a given dielectric constant,  $\epsilon$ . The boundary conditions for this model allow one to obtain a formally exact solution in terms of apparent surface charges only, and a very effective way of getting this solution is based on the use of the Green operators, which is the strategy exploited in standard PCM. In parallel with this possible solution, we can define other strategies. We examine two of these alternative methods, both now implemented in the same QM framework of PCM, the first exploiting different types of Green functions, and the second using other operators.

The first method has its origin in the proposal made by Klamt and Schüürman<sup>4</sup> of replacing the boundary conditions as expressed for a dielectric medium with those specific for a conductor (for which  $\epsilon = \infty$ ), and then introducing an empirical correction to come back to the original dielectric medium. This method, called COSMO (conductor-like screening model), has been first formulated in a semiempirical QM version, and more recently extended to *ab initio* calculations.<sup>5</sup> Alternative *ab initio* versions of the same method have been given by Truong and Stefanovich<sup>6</sup> and, more recently, by Barone and Cossi.<sup>7</sup>

The second nonstandard method we examine, called IEF (integral equation formulation), has re-

cently been elaborated in by group.<sup>8,9</sup> It represents a generalization of the standard electrostatic problem, with the aid of new operators, never used before in quantum chemistry, for the solution of integral equations. This method may treat, with a single ASC formalism (i.e., without introducing further approximations) both the linear isotropic dielectric model (scalar and constant  $\epsilon$ ), and other more complex models such as dielectrics with large-scale anisotropies (e.g., liquid crystals) or with real charges diffuse in the bulk (i.e., ionic solutions). More details about these methods will be given later.

We have introduced three different procedures to treat the same electrostatic solvation problem to better analyze another source of errors, accompanying that due to discretization outlined previously. This further source of errors is present with different characteristics in all the cavity-exploiting methods in which it is assumed that the whole solute charge distribution,  $\rho_M$ , lies within the cavity boundaries. In QM calculations, this is not the case, as the electronic contribution to  $\rho_M$  fades away exponentially, while the cavity surface is roughly determined by the minimum distance approach of the solvent molecules to the solute. As this minimum distance comes out from a balance between attractive and repulsive forces, the latter being essentially dependent on the overlap between solute and solvent electronic clouds, there is always an inherent tail of solute electronic charge lying outside the cavity. We will call this phenomenon the *tail error*.

In ASC methods, there is a simple way of monitoring discretization and tail errors. According to the Gauss theorem, the sum of all the apparent charge,  $Q_\sigma(\text{theo})$ , has to be related to the solute net charge,  $Q_M = \sum_a Z_a - N^{el}$  (where  $Z_a$  are the nuclear charges and  $N^{el}$  the number of electrons), by the expression:

$$Q_\sigma(\text{theo}) = -\frac{\epsilon - 1}{\epsilon} Q_M \quad (1)$$

The difference between the theoretical and the computed value of the total apparent charge:

$$\Delta_\sigma = Q_\sigma(\text{theo}) - Q_\sigma(\text{comp}) \quad (2)$$

is the evidence of the combination of the discretization and the tail errors we have just quoted.

Since the first formulation of the PCM method<sup>10</sup> this possible discrepancy has been taken into account, and a numerical procedure has been proposed to eliminate its effects.

This and other, successive, corrections have been defined as a renormalization of the apparent point charges  $\{q_k\}$  placed on the tesserae. The rules for this process of normalization have been changed over the years, following the evolution of PCM itself and the development of other specific motivations, such as those related to the power of computers and the nature of the chemical problem under examination.

In the following sections we analyze four normalization procedures (N1, N2, N3, and N4, respectively) used in the past or still in use in standard PCM, and we also take into account their possible extension to COSMO and IEF methods.

The numerical comparisons we present regard two neutral-anion couples, and exploit the marginal freedom left in defining the cavity remarked on at the beginning of this section. We have stressed this freedom up to cavity sizes that usually cannot be recommended for standard calculations. Reducing the size of the cavity far beyond a recommended value means to amplify the extent of tail error and to emphasize the effects both errors have on the final output of the calculation.

Numerical studies of this type are necessary to check the validity of new procedures, as we have had the occasion to learn several times in the past. We consider the example given here instructive enough to be presented to a general audience, as it shows both limits and potentialities of the cavity approach, and can be used by potential users of programs exploiting this approach as a guide in exploring the marginal freedom left in the definition of the cavity.

To express this point more clearly, it is worth explaining the reasons that led us to select this specific set of examples.

One of the present investigators (J.P.), during his research stay in Pisa, was interested in the study of acidic properties of fluorine-substituted alcohols and acids. As an initial step he decided to reproduce the good results about acidic properties in unsubstituted alcohols previously obtained in Valencia with an earlier version of PCM (of iterative nature) exploiting the normalization procedure we denote as N1<sup>11</sup>; however, his results were poorer than the previous ones. The reason was quickly discovered: In the original study on unsubstituted alcohols, the investigators used a cavity far smaller than the standard PCM one, exploiting the marginal freedom previously mentioned and giving detailed justifications for this choice. In

Pisa, on the contrary, the results were obtained with a more recent PCM version (the so-called direct PCM) exploiting a different renormalization rule, here denoted as N2 (its meaning will be given in the following section as well as that of other  $Nx$  procedures). The results showed that the marginal freedom left for the definition of the cavity for anions in the case of the N2-direct PCM procedure was not sufficient for the magnitude of cavity changes done in Valencia with an N1-iterative PCM method. More details on this point and many other aspects related to the same problem will be given in what follows.

## Cavity Errors and Their Corrections in Various PCM Versions

### STANDARD PCM VERSION

The first PCM version,<sup>10</sup> and those implemented in the following years until 1994, used an iterative procedure in which the optimization of the apparent charges was inserted as an intermediate inner loop of the main SCF cycle. At each step  $m$ , the charges,  $q_k$ , were determined using, as a first guess, the value computed using the normal component of the total electric field obtained at the preceding step, namely:

$$q_k^m(\vec{s}_k) = -\frac{\epsilon - 1}{4\pi\epsilon} a_k \vec{E}^{m-1}(\vec{s}_k) \cdot \hat{n}_k \quad (3)$$

where  $a_k$  and  $\vec{s}_k$  represent the area and the geometrical center of tessera  $k$ , respectively, and  $\hat{n}_k$  the unit vector normal to the surface at point  $\vec{s}_k$ , then allowing mutual polarization among the apparent charges themselves.

The normalization correction was addressed to replace the charges obtained at the convergence of the inner cycle of mutual polarization, generally affected by errors, namely:

$$\sum_k q_k = Q_\sigma(\text{comp}) = Q_\sigma(\text{theo}) - \Delta_\sigma \quad (4)$$

by a new set  $\{q_k^{\text{nor}}\}$ , defined as:

$$\begin{aligned} (q_k^+)^{\text{nor}} &= q_k^+ [1 + \Delta_\sigma / (2\Sigma_+ q_k^+)] \\ (q_k^-)^{\text{nor}} &= q_k^- [1 + \Delta_\sigma / (2\Sigma_- q_k^-)] \end{aligned} \quad (5)$$

The superscripts  $+$  and  $-$  refer to the sign of the apparent charges, and the partial sums,  $\Sigma_+$  and  $\Sigma_-$ , are extended to positive and negative sets, respectively. This correction distributes on each  $q_k$

an extra charge,  $\Delta_\sigma$ , according to the sign and the magnitude of the uncorrected charge itself. This is a very simple recipe, with the aim of maintaining low computational costs (the PCM method was elaborated for computers available in 1979), but effective enough when the basis set used to describe the solute wave function does not contain a large number of diffuse functions, or when there are no special features in the solute charge distribution giving rise to some strong asymmetries. We label this correction as N1.

This is in brief the normalization procedure exploited in the PCM versions we have implemented and distributed in the computational packages known as MONSTERGAUSS,<sup>12</sup> HONDO7, and partially HONDO8.<sup>13</sup>

We also recall that the PCM version in Gaussian-94 release, now in distribution,<sup>14</sup> is based on an iterative procedure exploiting the same N1 renormalization procedure.

In 1994, a new formulation of PCM was introduced to obtain analytical expressions for the free energy derivatives and gradients with respect to nuclear coordinates. In this method, called direct PCM (the reader is referred to ref. 15 for a detailed presentation), the iterative formulation of the apparent surface charges is performed during the SCF cycle, so that, in a single run, one obtains the solute wave function and the solvation charges at convergence. In addition, the two physical sources of apparent charges (i.e., nuclei and electrons of the solute  $M$ ) are separated, and the system giving ASCs is defined with the aid of two sets of linear equations:

$$\begin{aligned} \mathbf{q}^N &= -\mathbf{A}\mathbf{D}^{-1}\mathbf{E}_n^N \\ \mathbf{q}^e &= -\mathbf{A}\mathbf{D}^{-1}\mathbf{E}_n^e \end{aligned} \quad (6)$$

where:  $\mathbf{q}^N$  and  $\mathbf{q}^e$  are column vectors with size equal to the number of tesserae;  $\mathbf{A}$  is a diagonal square matrix containing the areas of tesserae ( $A_{kk} = a_k$ );  $\mathbf{E}_n^N$  and  $\mathbf{E}_n^e$  are column vectors collecting the normal components of the electric field exerted at the center of each tessera by solute nuclei and electrons, respectively; and  $\mathbf{D}$  is a square matrix with elements depending on  $\epsilon$ , on the geometry of the cavity, and on the analytical form of the electric field generated by the apparent charges. The expressions of these elements, which will be of some help in the following analysis, are:

$$\begin{aligned} D_{kk} &= 4\pi \left[ \epsilon / (\epsilon - 1) - \left( 1 - \sqrt{a_{kk} / 4\pi R_k^2} \right) / 2 \right] \\ D_{kl} &= a_l [(s_k - s_l) \cdot n(s_k) / |s_k - s_l|^3] \end{aligned} \quad (7)$$

The diagonal term of  $\mathbf{D}$ , which collects the contribution of the reaction field induced by the charge placed on tessera  $k$  on itself, is derived by the Gauss formula for an infinite charged plane with a correction term accounting for the curvature of the convex tessera belonging to the sphere of radius  $R_k$ . More details can be found in the source article.<sup>15</sup>

The separation of ASCs given in eq. (6) makes the cavity errors more critical. In ref. 15, we examined several options for the renormalization of charges, again seeking low computational cost. In fact, the direct PCM was addressed primarily to search critical points on the free energy hypersurface, with the perspective of many repeated calculations for each solute.

The procedure here called N2 corresponds to option (c), examined elsewhere.<sup>15</sup> The strategy for this procedure is based on the fact that  $\mathbf{q}^N$  charges are affected by the discretization error only, which, in opposition to the tail error, is constant during the whole calculation. The latter point makes the  $\mathbf{q}^N$  correction easy; in fact, once the total nuclear apparent charge  $Q_\sigma^N(comp)$ , given by the sum of all the  $\mathbf{q}^N$  charges, is computed, the error we make on it is completely known and can be definitely corrected by multiplying each charge by a constant factor defined as:

$$f^N = \frac{Q_\sigma^N(theo)}{Q_\sigma^N(comp)} \quad (8)$$

The same strategy is then applied to the complementary set of electronic apparent charges,  $\mathbf{q}^e$ , even if the parallel correction factor,  $f^e$ , has to be recomputed at each change of solute wave function. In fact, the error on  $Q_\sigma^e(comp)$  depends on the solute electronic tails, in addition to the discretization, and it changes during the SCF iteration procedure.

This second procedure is present in the last HONDO8, in all the GAMESS<sup>16</sup> versions of direct PCM we have distributed, as well as in a GAUSS-94 version we have implemented for our own use.<sup>17</sup> The same procedure will be present in the version we are now preparing for the next release of Gaussian, which will contain many improvements and additional features.

Both renormalization procedures N1 and N2 are based on the integral value of the charge, without any attempt at introducing corrections based on the explicit examination of each single tessera. As already noted, this choice has been dictated by the criteria of keeping low computational costs, even if for quite different reasons in the two cases.

The third procedure we consider, namely N3, represents a step toward more detailed corrections. It has been used in several studies, but never fully documented. Here, the discretization error in the  $\mathbf{q}^N$  set is corrected via the  $f^N$  factor as in N2. On the other hand, the  $\mathbf{q}^e$  charges are renormalized in two steps: first, they are multiplied by the factor  $f^N$  mentioned earlier (in fact, the discretization error can be assumed equal for both nuclear and electronic apparent charges), then the residual error due to the electronic tails is corrected in proportion to the solute electronic density  $\rho_M^e$  calculated on each tessera:

$$(q_k^e)^{nor} = f^N q_k^e + \frac{Q_\sigma^e(theo) - \sum_k f^N q_k^e}{\sum_k \rho_M^e(\vec{s}_k)} \rho_M^e(\vec{s}_k) \quad (9)$$

In such a way, the correction is greater in those parts of the cavity where the flux of electronic tails through the surface is more pronounced. N3 will be present in the new implementation of PCM for the next release of Gaussian.

In the fourth procedure, here called N4, the discretization errors are treated, once again, as in N2 and N3, whereas the effects due to the solute-escaped charge,  $Q_M^e(out)$ , are taken into account in the following way.<sup>3</sup>

The escaped charge is calculated exactly on the basis of the flux of the electric field through the cavity surface,  $S(C)$ :

$$Q_M^e(out) = - \left( N_e + \frac{1}{4\pi} \int_{S(C)} \vec{E}^e(\vec{s}) \cdot \hat{n}_s ds \right) \quad (10)$$

Being a real charge, it should give of its own a contribution to the solvent reaction field via a bulk apparent charge distribution,  $\rho_B(\vec{r})$ , spreading outside the cavity, so that:

$$\rho_B(\vec{r}) = - \frac{\epsilon - 1}{\epsilon} \rho_M^e(\vec{r}) \text{ in the bulk} \quad (11)$$

This contribution can be approximated in terms of an additional apparent surface charge distribution,  $\sigma_{eff}$ , expressed as:

$$\sigma_{eff}(\vec{s}) = - \frac{\epsilon - 1}{\epsilon} \frac{Q_M^e(out) \rho_M^e(\vec{s})}{\int_{S(C)} \rho_M^e(\vec{s}) ds} \quad (12)$$

This additional effective surface distribution can be treated exactly in the same way as the original one, and discretized in a further set of apparent charges  $\{q_{eff}\}$  by exploiting the same tessellation of the cavity surface into tesserae already used in the

PCM program. The important point to be stressed is that these new  $q_{eff}$  charges are not affected by the numerical errors analyzed thus far, because they do not depend on the fields generated by the other apparent charges, and do not need renormalization.

To better understand this important point, it is worth recalling that what we call discretization error in fact collects two different contributions. The first, of minor importance, is due to the use of surface piecewise constant functions instead of continuous ones; unpublished results obtained in our group have shown that the number of tesserae used in PCM is sufficient to well reproduce surface integrals of normal type. The second contribution, by far more important, is due to the fact that we describe the field each portion of apparent distribution charge spreading on tessera  $k$  exerts on itself and on the others, as a single point charge field. For example, in some specific cases, when the two interacting tesserae are close together, this approximation leads to errors of significant entity, and in general gives a quite rough description of the real situation. In other words, we can state that the discretization error is almost exclusively due to this second contribution.

More details on this point and on the general features of method N4, which is present, together with the N2 option, in the PCM version distributed with the last release of GAMESS, can be found in Mennucci and Tomasi.<sup>3</sup> The same procedure will be included in a forthcoming release of Gaussian; however, it is not present in all previously distributed copies of PCM.

## COSMO-PCM METHOD

The PCM version, which will be implemented in the next release of Gaussian, will also allow the use of the COSMO procedure within the QM framework of PCM.<sup>7</sup>

This new option has been implemented on the basis of the original elaboration given by Klamt and Schuurman,<sup>4</sup> but without using their computer codes (of which we have no direct knowledge). This basic reformulation has been formally recast in the PCM formulation, and here we give a short summary.

COSMO is based on a screening conductor theory. In our framework of solute  $M$  placed in a cavity inside the medium, now represented by a conductor, the boundary condition to be fulfilled is that the total potential,  $V$ , cancels out on the sur-

face,  $S(C)$ , of the cavity:

$$V(\vec{s}) = V_M(\vec{s}) + V_\sigma(\vec{s}) = V_M(\vec{s}) + \sum_k^K \frac{q_k(\vec{s}_k)}{|\vec{s} - \vec{s}_k|} = 0 \quad \forall \vec{s} \in S(C) \quad (13)$$

where we have exploited the same partition of the cavity surface into tesserae, which allows one to discretize the surface charge distribution,  $\sigma$ , into a set of  $K$  point charges.

By following the strategy already used in the PCM method, from eq. (13) we can express the basic system giving the apparent COSMO charges in the following matrix formalism:

$$\mathbf{Q} = -\mathbf{A}\mathbf{B}^{-1}\mathbf{V} \quad (14)$$

where the column matrix,  $\mathbf{V}$ , of dimension equal to the number,  $K$ , of tesserae, contains the solute electrostatic potential on each tessera, and the elements of the  $(K \times K)$  matrix  $\mathbf{B}$  are:

$$B_{kk} = 1.07a_k\sqrt{4\pi/a_k} \quad (15)$$

$$B_{kl} = a_l/|s_k - s_l|$$

where the expression for the diagonal term has been approximately derived from that of a homogeneously charged sphere.

The capital letter for the matrix containing the apparent charges stresses that the latter are derived for a real conductor, for which  $\epsilon = \infty$ ; if the COSMO model is used to simulate a solvent with dielectric constant,  $\epsilon$ , these apparent charges have to be scaled. This correction can be done in terms of a constant factor,  $f^C$ , which has a value not formally derived from the theory but based on some physical justifications.

Klamt suggests a form of the type  $(\epsilon - 1)/(\epsilon + k)$ , where  $k$  is a number ranging from 0 to 2, to be fixed by comparison with the values found for simple analytical cases: he uses the factor 0.5.<sup>4,5</sup> Barone and Cossi<sup>7</sup> use the expression  $f^C = (\epsilon - 1)/\epsilon$ , justifying this choice with the argument that the corrected apparent charges must satisfy the Gauss relationship [see eq. (1)], similar to those computed directly using a dielectric model. It should be added that, for highly polar solvents, like water, the definitions proposed by Klamt and by Barone and Cossi are almost equivalent. In what follows we exploit the second definition, which is in line with the normalization procedures we examined earlier in this study.

Thus, by exploiting the already defined partition into electrons and nuclei-induced apparent

charges, the two sets of charges to be used are:

$$\begin{aligned} \mathbf{q}^N &= -\frac{\epsilon - 1}{\epsilon} \mathbf{A} \mathbf{B}^{-1} \mathbf{V}^N \\ \mathbf{q}^e &= -\frac{\epsilon - 1}{\epsilon} \mathbf{A} \mathbf{B}^{-1} \mathbf{V}^e \end{aligned} \quad (16)$$

At this point, COSMO calculations can be performed by using exactly the same program as for PCM calculations.

We have checked the validity of the correction exploited in eq. (16) by examining, in several solutes, the value of charges  $q_k^n$  and  $q_k^e$  at each tessera,  $k$ . For solvents with a large dielectric constant, the factor  $(\epsilon - 1)/\epsilon$  seems to be sufficient, whereas, for solvents at low  $\epsilon$  (e.g., in the range 2–10), the problem must be re-examined.

COSMO too is affected by the problem of possible discrepancies between computed apparent charges and those derived from the Gauss law; once again, this condition is unfulfilled, for both numerical and physical reasons. It can be shown, however, that the cavity errors are smaller in COSMO-PCM than in standard PCM. The main reason is due to the use, in COSMO, of boundary conditions expressed in terms of electrostatic potential instead of electric field, as done in PCM.

A display of  $\Delta_\sigma^N$  and  $\Delta_\sigma^e$  values obtained with COSMO-PCM for a number of neutral solutes has been given by Barone and Cossi.<sup>7</sup> From that work we draw the mean errors over 19 compounds [HF-6.311G(*d*, *p*) values computed with Gaussian-94], namely  $\bar{\Delta}_\sigma^N = -0.0014e$  and  $\bar{\Delta}_\sigma^e = +0.020e$ . The ratio of the two errors is similar to that found using the correct boundary conditions for the dielectric case (i.e., in the PCM), but the absolute values are lower by a factor of about 20.

The need of introducing correction factors to the apparent charges seems to be less impelling, and in the following section we give some numerical evidence on this point.

Correction of cavity errors is beneficial, however, even for COSMO, as will be documented in a future study. It is convenient to introduce corrections for both types of errors, and this has been done thus far using N2 and N3 techniques. We are now working on implementing the N4 technique in the COSMO version, to be added to the PCM we are preparing for Gaussian.

To complement the information about COSMO correction procedures, we note that, in a recent study, Klamt and Jonas<sup>20</sup> gave a further solution for the tail errors in the original COSMO formula-

tion, which, however, disregards discretization errors.

The general concept is as follows: After a normal COSMO calculation, an additional cavity is constructed around the solute molecule lying at an appropriate distance ( $R_{out}$ ) further away from the original one to enclose entirely the full electron density of the solute (a distance of about 1 Å should be enough). Once this new cavity has been partitioned into  $K$  segments in exact correspondence with those of the original one, the potential,  $V'$ , arising from the solute and the primary set of apparent charges on the inner cavity is evaluated on the new tesserae of the outer cavity. In perfect analogy with the standard COSMO algorithm, by exploiting eq. (14) with  $V'$  and a new  $\mathbf{B}'$  matrix evaluated on the new cavity, one can define an additional set of apparent charges,  $\mathbf{q}'$ , which are then added to the primary ones, thanks to the correspondence in the tesserae of the two cavity surfaces. The apparent charges,  $\mathbf{q}'' = \mathbf{q} + \mathbf{q}'$ , thus obtained, can then be used in the evaluation of the final interaction energy. More details, and a generous display of numerical results, can be found elsewhere.<sup>20</sup>

## IEF-PCM METHOD

This recent method is based on the use of operators largely exploited in the theory of integral equations, but not used so far in computational and theoretical chemistry.

The mathematical foundations are given in ref. 8, and the first examples of chemical applications in ref. 9. Here, we do not try to give a detailed description of the method, and we limit ourselves to stress few points.

The concept of cavity and of its tessellation is conserved. Instead of starting from the boundary conditions, such as in the standard PCM and in COSMO-PCM, addressed and limited to specific media (i.e., homogeneous isotropic dielectrics and conductors, respectively), it is convenient to start from the basic Laplace and Poisson equations, introducing here the specification on the system under scrutiny. The IEF formalism is in fact able to treat a larger class of electrostatic problems, among which the homogeneous isotropic dielectric and the conductor are just two particular cases.

In analogy with the previous ASC procedures, in the computational implementation of IEF we exploit a tessellation of the cavity surface into  $K$  tesserae, and approximate the charge density,  $\sigma$ ,

by a piecewise constant function (i.e., a function constant on each tessera). In this approximation, the relations giving the apparent charges can be expressed in the form of matrix equations:

$$\mathbf{q} = -\mathbf{A}\mathbf{C}^{-1}\mathbf{g} \quad (17)$$

where  $\mathbf{q}$  is the column vector containing the apparent charges on a single tessera,  $\mathbf{C}$  is a  $K \times K$  matrix,  $\mathbf{A}$  is the usual diagonal matrix of tesserae areas, and  $\mathbf{g}$  is a column vector depending on the solute charge distribution,  $\rho_M$ . The explicit expressions of the IEF main matrices are:

$$\begin{aligned} \mathbf{C} &= (\mathbf{A}/2 - \mathbf{D}_e)\mathbf{A}^{-1}\mathbf{S}_i + \mathbf{S}_e\mathbf{A}^{-1}(\mathbf{A}/2 + \mathbf{D}_i^*) \\ \mathbf{g} &= (\mathbf{A}/2 - \mathbf{D}_e)\mathbf{V} - \mathbf{S}_e\mathbf{E}_n \end{aligned} \quad (18)$$

We have already given the definition of the electrostatic matrix,  $\mathbf{V}$ , and the corresponding one for the normal components of the field,  $\mathbf{E}_n$  (both computed at the centers of the tesserae). Matrix  $\mathbf{C}$ , which corresponds to matrix  $\mathbf{D}$  in PCM and to matrix  $\mathbf{B}$  in COSMO, is composed of several matrices, each corresponding to different operators. We add that, in the IEF method, we can also exploit the usual partition into electrons and nuclei-induced apparent charges, as obtained by evaluating the electronic and nuclear components of the potential,  $\mathbf{V}$ , and the field,  $\mathbf{E}_n$ , matrices defining  $\mathbf{g}$ :

$$\begin{aligned} \mathbf{q}^N &= -\mathbf{A}\mathbf{C}^{-1}\mathbf{g}^N \\ \mathbf{q}^e &= -\mathbf{A}\mathbf{C}^{-1}\mathbf{g}^e \end{aligned} \quad (19)$$

In what follows we report the specific expressions of the exploited matrices as they are derived for the isotropic case. In fact, for the scope of the present work, it is not necessary to give the complements one needs to treat nonisotropic cases or ionic solutions, here we limit ourselves to recall that the operators defined for the inner space of the cavity (i.e., those with index  $i$ .) remain unchanged in all the applications, whereas while those for the external part (index  $e$ ) have to be redefined in each specific system.

In the isotropic limit, we have:

$$\begin{aligned} (S_i)_{kk} &= 1.07a_k\sqrt{4\pi a_k} \\ (S_i)_{kl} &= a_k a_l / |\vec{s}_k - \vec{s}_l| \end{aligned} \quad (20)$$

and:

$$\begin{aligned} (D_i)_{kk} &= 1.07a_k\sqrt{\pi a_k/R_k^2} \\ (D_i)_{kl} &= a_k a_l / \left[ (\vec{s}_k - \vec{s}_l) \cdot \hat{n}(\vec{s}_l) / |\vec{s}_k - \vec{s}_l|^3 \right] \end{aligned} \quad (21)$$

where  $R_k$  is the radius of the sphere on which tessera  $k$  is placed. The parallel  $\mathbf{S}_e$  and  $\mathbf{D}_e$  matrices are easily derived from the relations (valid only in the isotropic case):  $\mathbf{S}_e = \mathbf{S}_i/\epsilon$ , and  $\mathbf{D}_e = \mathbf{D}_i$ .

The IEF method presents both discretization and tail errors, but at the same reduced level as COSMO-PCM, and perhaps lower; in any case, it has been supplemented so far with the N2 renormalization procedure.

IEF-PCM has not yet been distributed, but we plan to include it in the material to be considered for a future release of Gaussian.

## Computational Example of Cavity Errors and Corrections

We report some results drawn from calculations on four solutes, namely ethanol, ethanolate anion, acetic acid, and acetate anion in a dielectric medium mimicking water ( $\epsilon = 78.39$ ), with the various methods we have presented in the previous section and with a systematic variation of a cavity parameter.

The calculations have been performed at the HF level with two basis sets [6-31G\* and 6-31G\*(*sp*), with the diffuse *sp* function, exponent 0.0845, on the oxygen atom only]. The geometries of the solute have been kept fixed at the optimum HF geometry *in vacuo*.

The radius of the sphere centered on the oxygen atom has been systematically varied in the range 1.2–2.8 Å. The other cavity parameters have been kept fixed at the values determined according to the PCM default options, namely 1.2 times the van der Waals radii, as given by Pauling.<sup>18</sup> We recall that there are other sets of recommended cavity parameters.<sup>7,17,19</sup>

Before going inside the analysis of the numerical data, we recall that PCM gives, as a primary energetic quantity, a free energy,  $G_{sol}$ , defined with respect to the hypothetical state of an unperturbed solvent and the solute represented as a set of separate and noninteracting electrons and nuclei. From this quantity one may derive a solvation free energy as the difference between  $G_{sol}$  and the parallel quantity *in vacuo*:

$$\Delta G_{sol} = G_{sol} - G_{vac}$$

As seen previously for the solute–solvent interaction terms,  $\Delta G_{sol}$  can also be partitioned into contributions of different physical origin, among which the electrostatic one is generally the most impor-



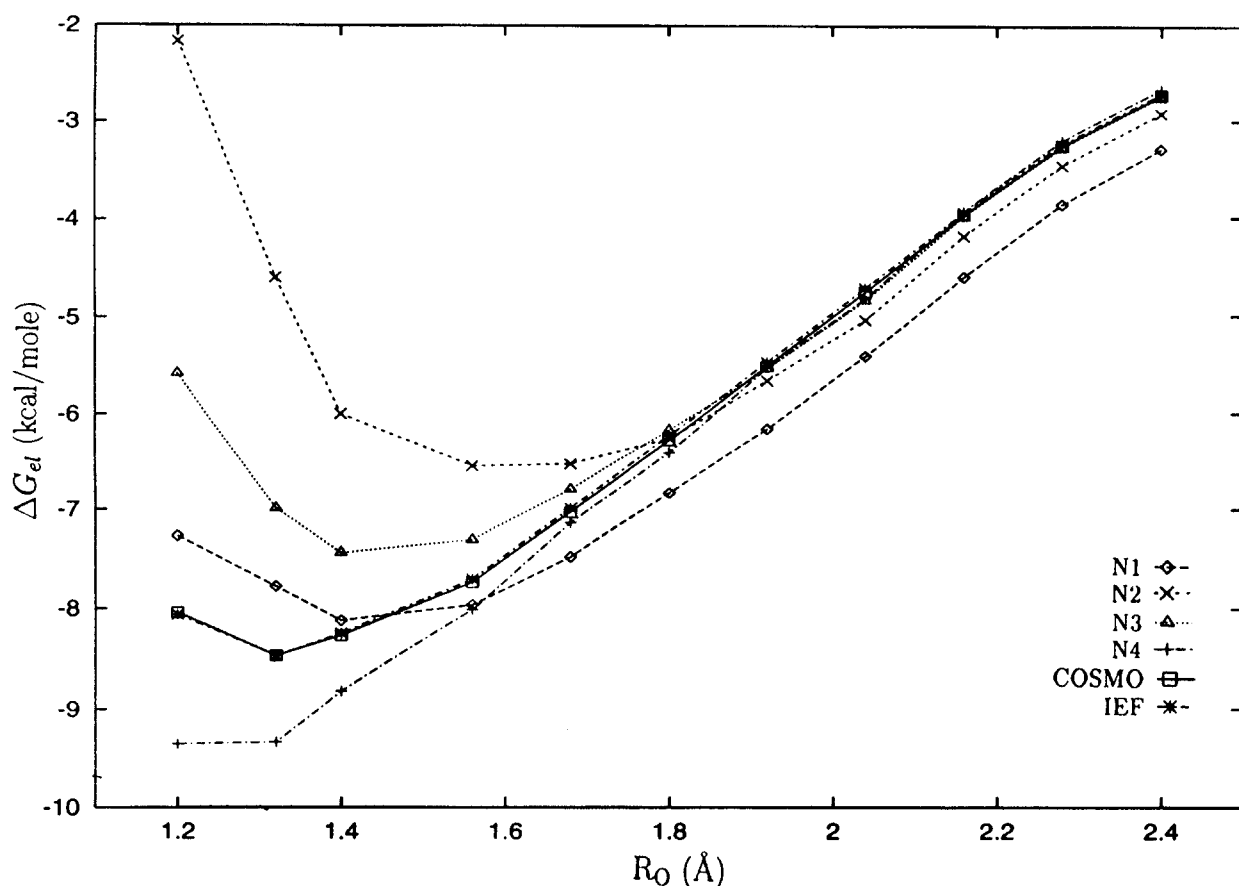
tant, at least for solutes in polar solvents (the remaining terms are called cavitation, repulsion, and dispersion). The procedures used in PCM to compute the other elements of  $\Delta G_{sol}$  can be found in several works, among them Tomasi and Persico.<sup>1</sup>

We limit ourselves to reporting  $\Delta G_{el}$  values, the only ones affected by the cavity errors described in the previous section; in this way we cannot make direct comparisons to experimental results, but this is of no real importance in this study. Suffice it to say that the relations between neutral/anion couples are well described by the continuous, PCM-like methods.

A progressive reduction of the  $R_0$  radius in the selected range should give more and more negative values  $\Delta G_{el}$  values. The deviations with respect to this trend, especially when the radius is smaller, indicate an insufficient correction of the cavity errors. There may also be small deviations from the linear behavior of the  $\Delta G_{el}$  curves in other, less extreme regions—these are due to an-

other type of error we have not discussed in this work, again related to the discretization procedure. At some geometries, it may be that, at the intersection of two or more spheres forming the cavity, there are tesserae of small and/or very irregular shape, and these may give rise to irregularities.

Perhaps it is worth recalling that the tessellation in PCM is derived from a preliminary uniform tessellation of each sphere in terms of the vertices of a regular polyhedron inscribed in it (usually a pentakis dodecahedron is used, in which case the total number of tesserae on each sphere is 60). When the spheres are put together, those portions of the surface (the tesserae) that are partially or completely buried inside the resulting molecular cavity are deleted, partially or completely.<sup>21,22</sup> In the case of partial deletion the resulting tessera has an irregular shape, and can sometimes even be divided into two portions. PCM programs signal the occurrence of these unfortunate cases, which



**FIGURE 1.** Electrostatic contribution to the hydration free energy (kcal/mol) of ethanol with respect to the radius of the sphere centered on the oxygen atom. The calculations have been performed at the HF level with a 6-31G\*(sp) basis set.

can be eliminated by resorting to a different tessellation of the original spheres. This point has no particular relevance for calculations at fixed geometry, but it creates problems in the definition of free energy gradients. PCM versions addressed to derivative and gradient calculations have special features to eliminate these drawbacks.

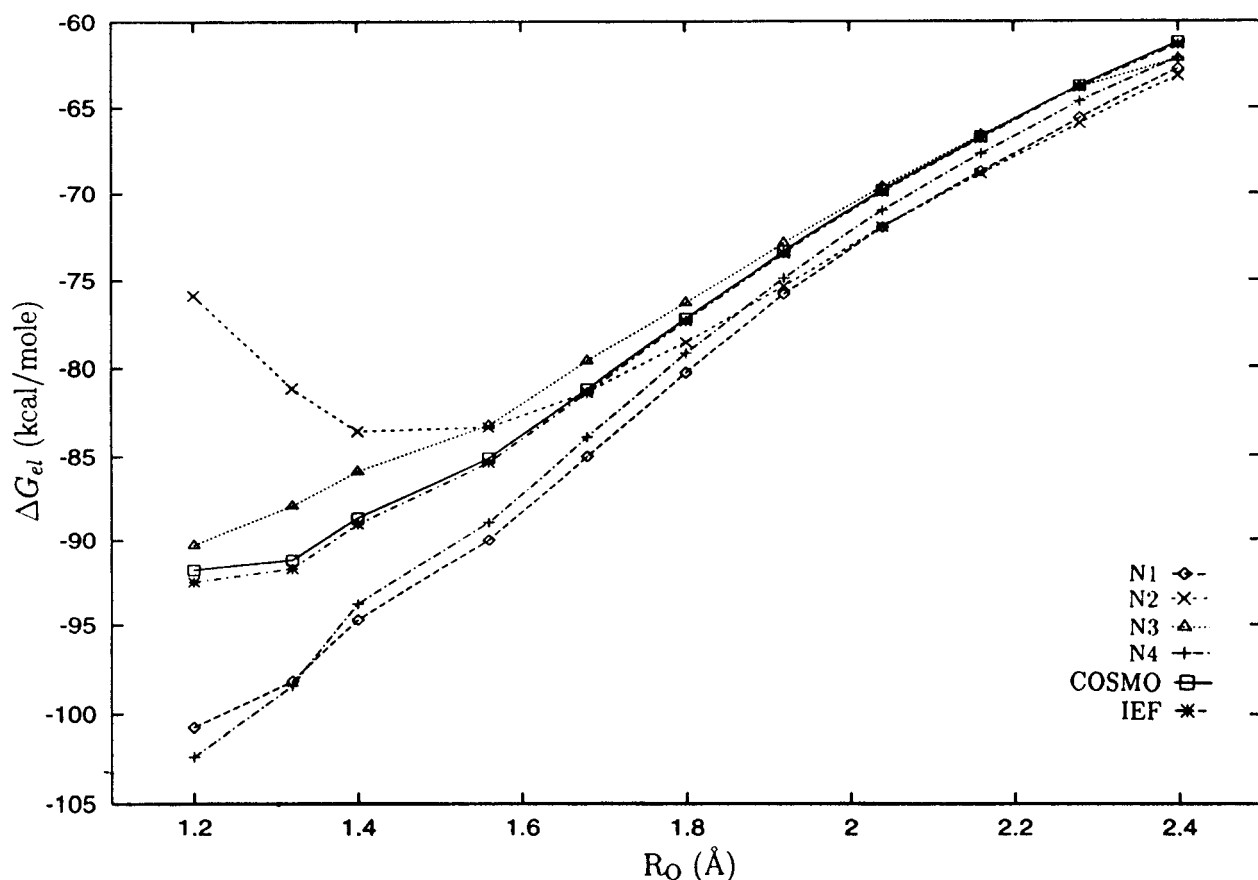
We can now examine in detail the results displayed in Figures 1–4. The data reported refer to the larger basis set [i.e., 6-31G\*(*sp*)] only; in fact, parallel results obtained with the other basis set (i.e., 6-31G\*), even if quite different in magnitude, show general trends almost equal to the previous ones. For the sake of completeness, in Tables I and II we report a comparison between data obtained with the two basis sets for a single-solute, acetic anion, for which the differences are the largest.

One must remember that the cavity errors become larger and more difficult to correct when the basis set contains diffuse functions. From the numerical data of Figures 1–4 it appears that the

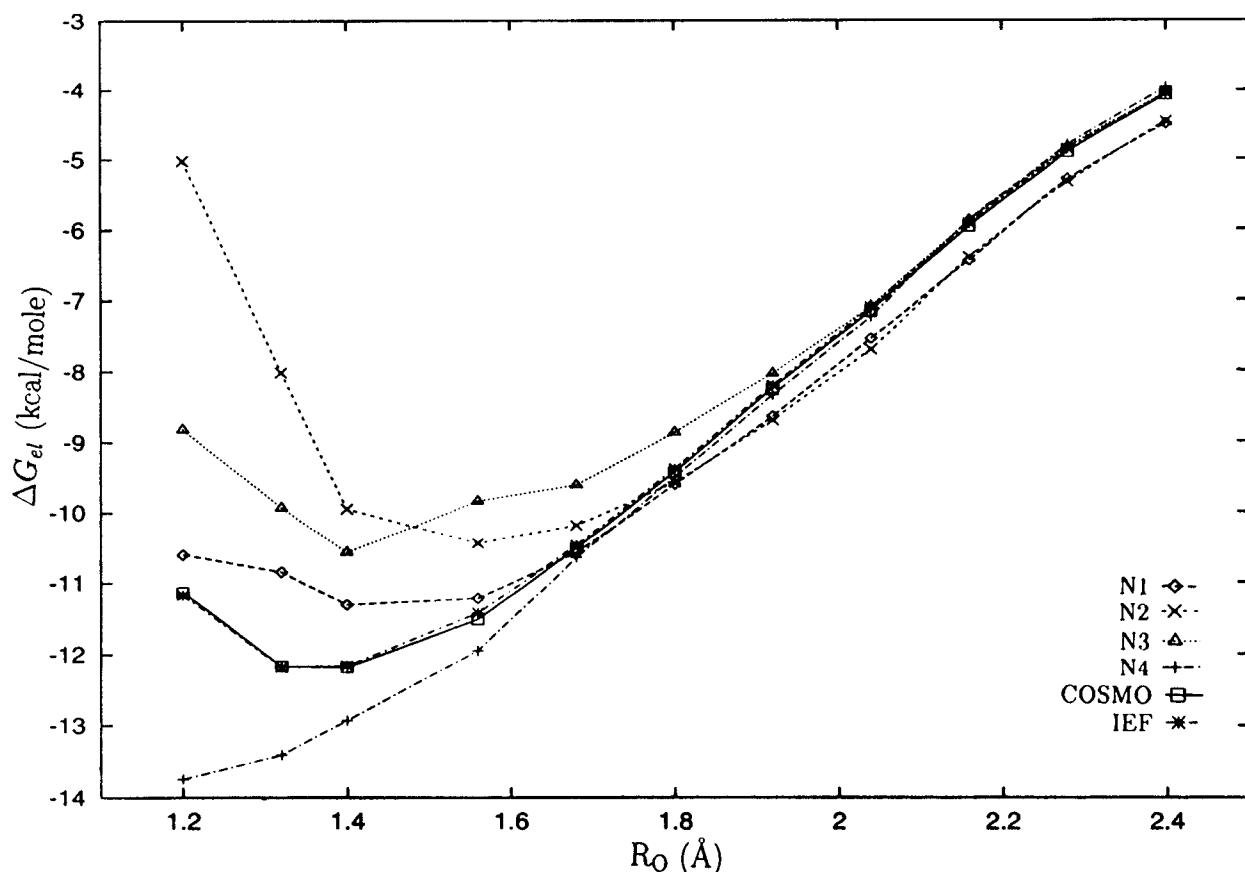
renormalization of N2 has the most limited range of applicability, which clarifies what was briefly noted in the Introduction, namely that there was divergence among N1 iterative PCM and N2 direct PCM. The value of  $R_0$  used for the enolates in ref. 11 was equal to 1.4 Å; that is, a value at which the N2 procedure is no longer valid, whereas, the N1, which was the procedure used in their study, continues to work.

In general, the ranges of validity of N1 and N3 are comparable, even if, for very small  $R_0$  values, the N1 iterative PCM procedures diverge, whereas, results given by the N3 direct PCM are still within reasonable errors.

The N4 procedure is almost completely free from errors due to solute tails. The only irregular value, namely that corresponding to  $R_0 = 1.2$  Å for ethanol, probably indicates the presence of an additional less important error which can be related to the use of constant  $f^N$  factors for the normalization of nuclear apparent charges. We



**FIGURE 2.** Electrostatic contribution to the hydration free energy (in kcal/mol) of ethanolate anion with respect to the radius of the sphere centered on the oxygen atom. The calculations have been performed at the HF level with a 6-31G\*(*sp*) basis set.



**FIGURE 3.** Electrostatic contribution to the hydration free energy (in kcal / mol) of acetic acid with respect to the radius of the sphere centered on the oxygen atom. The calculations have been performed at the HF level with a 6-31G\*(sp) basis set.

have found similar possibilities in other comparable extreme cases, but we do not consider it necessary to introduce further corrections for such errors, which occur only in very extreme calculations and are never performed in standard practice.

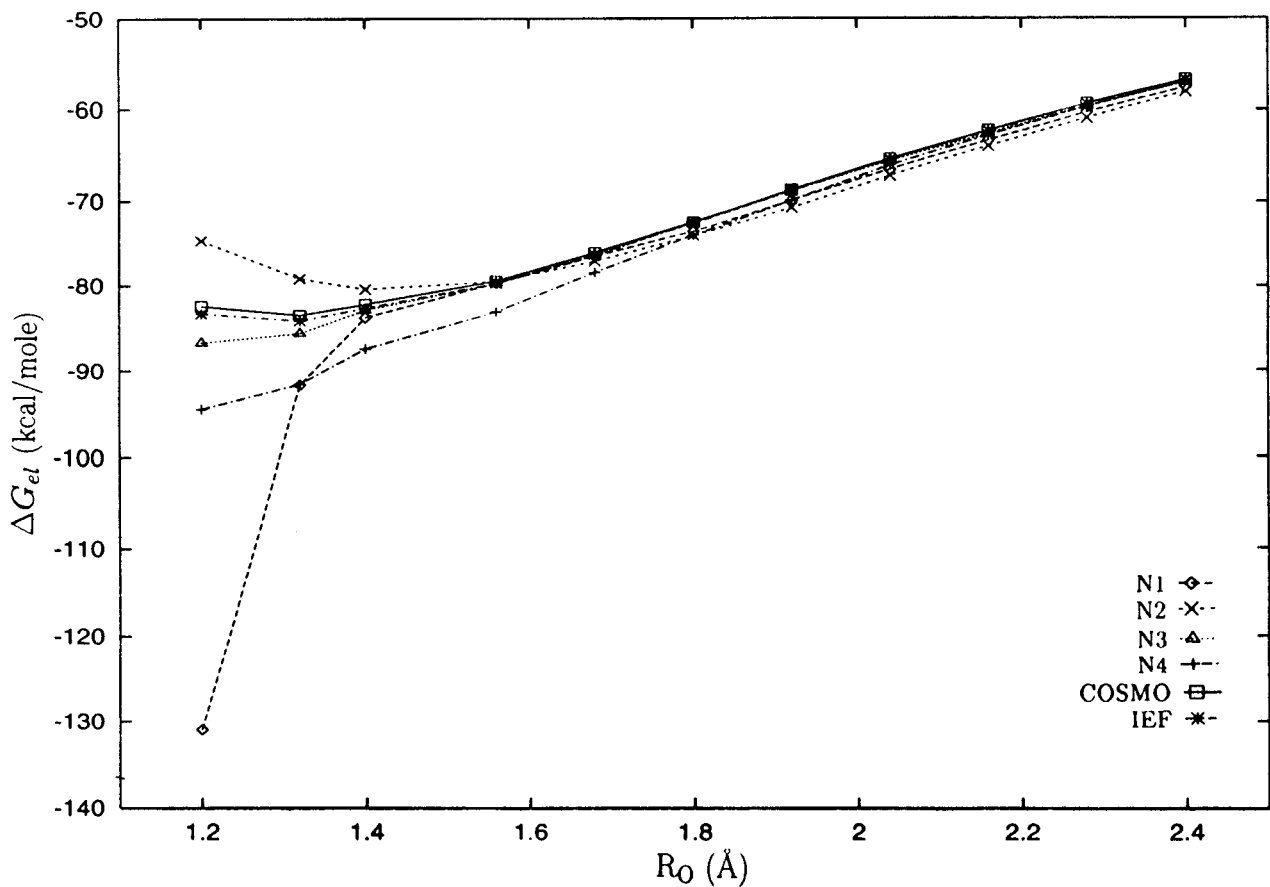
Furthermore, the very unusual value obtained by the N1 method for the acetate ion at 1.2 Å can be ascribed to numerical drawbacks not related to the problem being investigated.

The COSMO-PCM and IEF-PCM results reported here were obtained without corrections of any type, and they show an almost perfect correspondence. Only at very low  $R_0$  values is there evidence that the cavity errors also become effective for these less sensitive methods. As we have already stressed, these are extreme cases never encountered in routine calculations on systems of a similar chemical nature (the recommended range of variation of  $R_0$  is 1.68–1.8 Å); hence, we can state that the trend shown by the two methods is

generally very good even when not supported by the normalization procedures. Anyway, we can recall that, in some other cases, less extreme but still dangerous—especially for the phenomenon of the escaped charge—standard renormalization procedures can be exploited effectively using these methods.

A last remark about the various results reported in the figures concerns N1 calculations for ethanol. This curve is consistently lower than the others. As already noted, the N1 results displayed here refer to a MONSTERGAUSS iterative PCM version, which keeps the number of SCF iteration cycles limited, as suggested by previous studies. By increasing the number of cycles we should recover almost complete agreement between this curve with the others in the region of medium and high  $R_0$  values.

The present results show that the calculated  $\Delta G_{el}$  values can be changed both by adjusting the cavity dimensions, and by correcting the escaped



**FIGURE 4.** Electrostatic contribution to the hydration free energy (in kcal / mol) of acetic anion with respect to the radius of the sphere centered on the oxygen atom. The calculations have been performed at the HF level with a 6-31G\*(*sp*) basis set.

**TABLE I.**  
**ΔG<sub>el</sub> Values (kcal / mol) of Acetate Anion, Obtained With the Four Nx version of PCM at Various Oxygen Atom Radius Values.<sup>a</sup>**

<i>R</i> <sub>0</sub> (Å)	N1	N2	N3	N4
1.2	−130.98 (−104.68)	−74.67 (−78.83)	−86.66 (−88.57)	−94.57 (−95.30)
1.32	−91.70 (−88.14)	−79.19 (−82.14)	−85.57 (−87.63)	−91.62 (−91.33)
1.4	−83.71 (−83.17)	−80.41 (−82.29)	−82.86 (−82.77)	−87.39 (−86.79)
1.56	−79.73 (−79.66)	−79.51 (−80.19)	−79.74 (−80.36)	−83.04 (−81.90)
1.68	−76.48 (−76.10)	−77.10 (−77.06)	−76.37 (−75.57)	−78.43 (−77.14)
1.8	−73.49 (−72.93)	−74.02 (−76.19)	−72.44 (−73.83)	−73.97 (−72.62)
1.92	−69.87 (−68.88)	−70.69 (−69.47)	−68.82 (−67.59)	−69.87 (−68.54)
2.04	−66.48 (−65.28)	−67.15 (−65.92)	−65.55 (−64.31)	−66.03 (−64.66)
2.16	−63.27 (−61.94)	−63.93 (−62.94)	−62.55 (−61.32)	−62.73 (−61.45)
2.28	−60.29 (−59.01)	−60.87 (−59.63)	−59.66 (−58.55)	−59.70 (−58.56)
2.4	−57.60 (−56.39)	−58.09 (−56.95)	−57.05 (−56.03)	−57.03 (−56.04)

<sup>a</sup>Each column reports data obtained both with 6-31G\*(*sp*) and 6-31G\* basis sets. The latter are reported in parentheses.

**TABLE II.**  
 $\Delta G_{el}$  Values (kcal / mol) of Acetate Anion, Obtained with COSMO-PCM and IEF-PCM Methods, at Various Oxygen Atom Radius Values.<sup>a</sup>

$R_O(\text{\AA})$	COSMO	IEF
1.2	-82.39 (-85.96)	-83.25 (-87.10)
1.32	-83.45 (-85.62)	-84.08 (-86.63)
1.4	-82.17 (-83.11)	-82.62 (-83.96)
1.56	-79.44 (-79.43)	-79.74 (-80.09)
1.68	-76.06 (-75.35)	-76.27 (-75.92)
1.8	-72.35 (-71.24)	-72.49 (-71.72)
1.92	-68.71 (-67.43)	-68.79 (-67.78)
2.04	-65.33 (-63.98)	-65.41 (-64.31)
2.16	-62.20 (-60.93)	-62.27 (-61.20)
2.28	-59.35 (-58.17)	-59.41 (-58.40)
2.4	-56.77 (-55.71)	-56.83 (-55.93)

<sup>a</sup>Each column reports data obtained with 6-31G\*(sp) and 6-31G\* basis sets (in parentheses), without any renormalization of the charges.

charge errors with various methods; however, the physical justification for these procedures is clearly very different. Many PCM calculations are performed with standard atomic radii sets (namely Bondi's<sup>23</sup> or Pauling's<sup>18</sup> radii scaled by 1.2). Even if all the normalization procedures work quite well in this range of radii, we suggest the use of methods more physically tested (i.e., N3 or N4). In fact, these methods are likely to provide better descriptions of solute electronic distributions, whereas, in this case, the quality of  $\Delta G_{el}$ s depends on the normalization method used. The situation is different for a procedure recently developed to build "optimized" cavities according to the solute molecular topology<sup>24</sup> and applied to PCM, COSMO-PCM, and IEF-PCM. (The accurate N4 normalization procedure has been used during the optimization of the geometrical parameters of this cavity model.) In this latter case, the N4 procedure not only ensures a better description of the wave function, but it also gives a closer agreement with the experimental data, at least for PCM calculations on ionic solutes.

## Conclusions

We have examined two errors of general occurrence in ASC continuum methods, by exploiting results given by very different techniques, including the most recent ones, COSMO-PCM and IEF-PCM, not yet distributed.

The exposition is accompanied by analysis of numerical results drawn from a rather formal problem, that of the electrostatic solvation energy in couples of neutral/anion systems in which a single cavity parameter is systematically changed.

The analysis reported here is addressed to provide some suggestions for potential users about the freedom they have in fixing cavity parameters to nonstandard values and an overview of present and future PCM versions.

Obviously an analysis of this kind does not exhaust the subject of checking cavity errors—there are different problems requiring separate analyses; for example, the application of PCM to the calculation of static and dynamic hyperpolarizabilities, the calculation of electronic excited states, the extensions of the model to dynamical problems such as those occurring in chemical reactions of thermal and especially photochemical nature. We have quoted here some examples for which there are PCM studies already available (by several investigators) or still in preparation.

A final comment regards other continuum solvation models not based on the ASC approximation, but using a cavity. The most outstanding versions now in use include the SCRF set of programs elaborated by Rivail's group,<sup>25</sup> and the AMSOL method elaborated by Cramer and Truhlar.<sup>26</sup>

We do not intend to make comparisons among PCM-like, SCRF, and AMSOL methods regarding the quality of results one can obtain from each and the specific range of applicability, and we limit ourselves to the aspects related to cavity errors. Both SCRF and AMSOL are free from discretization errors as they do not exploit tesserae.

SCRF methods use a multipolar expansion of the electrostatic potential, assuming that the whole solute charge lies within the cavity. The tail error is not formally present as there is no analog of the Gauss theorem to signal it. It must also be noted that, in these methods, the whole charge is contracted in the point multipoles used for the expansion. There is, however, another source of errors that parallels the tail one. Multipolar expansions are valid if the points to which the method is applied in computing interactions lie completely outside of the sphere encircling the source charge distribution. This is a severe source of errors for cavities with irregular shape, to be alleviated by the use of multicenter expansions, each regarding a charge distribution with a presumably more limited spatial distribution.

AMSOL methods belong to the family of generalized Born methods, in which the charges are

centered on the nuclei: in other words, an extreme case of multicenter multipole expansion. The inherently limited nature of AMSOL, which exploits semiempirical QM calculations and adds other semiempirical parameters to describe the solvent effects, reduces the occurrence of cavity errors to a subject of no immediate interest.

There are other recent *ab initio* QM solvation programs that use continuum solvent models and cavities, but exploit 3D integration techniques (FEM or FDM approaches<sup>1</sup>) to solve the electrostatic problem.<sup>27,28</sup>

We have no direct experience with these programs, in which there are no error tails, but with discretization errors presumably of greater entity with respect to those considered here. The most evident discretization errors have been corrected in the previous classical versions of these methods (see, e.g., ref. 29).

Analogous errors are present in the PCM-FEM methods we have developed in the past,<sup>30,31</sup> and are still using,<sup>32</sup> but we are now replacing them with the more effective IEF-PCM parallels.

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